Docket No.: 081722-0362 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Customer Number: 83729
Zhi-Jie Ni, et al.	:	Confirmation Number: 9706
Application No.: 10/576,045	:	Group Art Unit: 1626
Filed: April 14, 2006	:	Examiner: Loewe, Sun Jae Y.

For: COMPOSITIONS AND METHODS FOR VIRAL INHIBITION

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being electronically-transmitted to the United States Patent and Trademark Office on **Aug 10, 2010.**
/Lori Ford/
Lori Ford

SUBMISSION ACCOMPANYING REQUEST FOR CONTINUED EXAMINATION UNDER 37 CFR 1.114

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Commissioner for Patents
P.O. Box 1450
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Sir:

Please find the additional remarks to be submitted along with the request for continued examination. Remarks begin on page 2 of this paper.

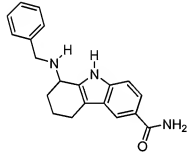
REMARKS

Claims 1-104 are pending. Claims 60, 65, 66, 84-88, and 90 are under examination. Applicants respectfully request reconsideration of the claims in view of the further Remarks below in conjunction with those previously of record.

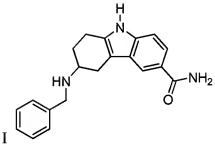
Rejection under 35 U.S.C. §103

The rejection of claims 60, 65, 84, 87, and 90 under 35 U.S.C. §103(a) as allegedly being obvious over King et al. (caplus an 1993:212888) is respectfully traversed.

The basis of the alleged obviousness turns on the comparison of Compound I, a member of the presently claimed genus, with the compound of King et al., as shown below.



Compound I



King et al.

Legal Standard

The Federal Circuit has opined on the obviousness of chemical compounds in numerous decisions post-KSR and the following excerpts detail what is required in establishing a *prima facie* case of obviousness. The rejection set forth by the Examiner nominally relies on a premise of an "obvious to try" approach based on the King et al. compound as a starting point.

> An obviousness argument based on structural similarity between claimed and prior art compounds clearly depends on a preliminary finding that **one of ordinary skill in the art would have selected [the prior art compound] as a lead compound**. *The Proctor and Gamble Company v. Teva Pharmaceuticals USA, Inc.* Case Nos. 08-1404, -1405, -1406 (Fed. Cir., May 13, 2009) quoting Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492, F.3d at 1359 (Fed. Cir. 2007). emphasis added

> it remains necessary to identify **some reason that would have led a chemist to modify a known compound in a particular manner to establish**

> ***prima facie* obviousness** of a new claimed compound. Takeda 492 F.3d at 1350, 1357, emphasis added.
>
> The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem **and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp**." Takeda 492 F.3d quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), emphasis added.

In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358 (Fed. Cir. 2008), Ortho-McNeil's patent claimed the anticonvulsive drug topiramate. Mylan argued that anyone of ordinary skill in the art searching for a diabetes drug would necessarily find topiramate. The Federal Circuit found, however, that:

> [t]he record . . . **does not present a finite (and small in the context of the art) number of options easily traversed to show obviousness** . . . In this case, the record shows that a person of ordinary skill would not even be likely to start with [the compound selected by the inventor]. Beyond that step, however, the ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternatives) the exact route that produced topiramate as an intermediate. Even beyond that, the ordinary artisan in this field would have had to (at the time of invention without any clue of potential utility of topiramate) stop at that intermediate and test it for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes). In sum, this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness.

In *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008), the Federal Circuit articulated the post-*KSR* application of the "obvious to try" approach as:

> determine if there are **"reasons for narrowing the prior art universe to a 'finite number of identified, predictable solutions[,]'** [citation to *KSR* and *Ortho-McNeil* omitted] If so, "this 'easily traversed, small and finite number of alternatives . . . might support an inference of obviousness.'"

The Court in *Eisai* went on to say:

> **To the extent an art is unpredictable, as the chemical arts often are**, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because **potential solutions are less likely to be genuinely predictable**.

Advisory Action

The Examiner has upheld the allegation of obviousness of Compound I in view of the King et al. compound in an Advisory Action having a mailing date of June 4, 2010. In the Advisory Action the Examiner alleges that the subject matter examined was directed to the

product, not method of using. The Examiner alleges that, because the prior art "lead" compound has *some* kind of pharmacological activity, it renders obvious the present composition claims despite having a different pharmacological activity as described in the present application.

In response, Applicants respectfully submit that, if the selection of a lead compound is divorced from its intended utility, then the world of prior art should be considered every compound ever developed with any pharmacological activity. This logic fails to narrow **the prior art universe to a 'finite number of identified, predictable solutions**," (*Eisai supra*) because one is confronted with a nearly infinite array of starting compounds. Applicants respectfully point out that this logic also presumes that the Applicants had no intention of targeting the asserted utility. Applicants suggest that one skilled in the art interested in developing new antiviral agents would first look to existing structures having the desired utility for guidance. To put this another way, even if the Applicants were omniscient with respect to every compound ever developed, by what rationale would they select King et al. and conclude this was good a starting point for starting their antiviral program?

Even assuming *arguendo* that the utility of King et al. coincided with that of the present application, the two isomeric compounds are not obvious for at least the further reasons set forth below.

The Examiner alleges the genus presented in King et al. is compact and modification for the development of alternate compounds is reasonable to one skilled in the art for the purpose of the same utility, i.e. the treatment of headache as described in King et al. The Examiner alleges that there would be a reasonable expectation of success based on minor structural modification, such that the skilled artisan would not expect to alter the activity significantly.

In response, Applicants assert that 1) the number of possible "minor" modifications are without limitation; 2) there is no guidance in the cited art governing what types of changes to make; 3) the differences between Compound I and the compound of King et al. represent very large changes, not minor changes; and 4) the Examiner's opinion that there is a reasonable expectation of success is counter to the case law with respect to genuine predictability in the chemical arts.

1. The number of possible "minor" modifications are without limitation.

The Examiner suggests that one skilled in the art would have reason to explore structural variation based on a lead compound for the development of further compounds having the same utility. If for argument's sake one takes this to be true, then one skilled in the art of medicinal chemistry might be inclined to use any and all tools at their disposal including rational design as well as combinatorial optimization. Minor modification might include not only ring-walking the benyzlated amine, as required to arrive Compound I, but also ring walking of the amide. In addition to ring-walking, one might swap out the amide group or the benzyl amine group for other structures as well. Any structural substitution for these groups might also be ring-walked. Any of the three NH groups in the King et al. compound could also be utilized as a springboard for minor changes in structure. Substituents, as taught in King et al., include, alkyl, aralkyl, alkoxy, aralkoxy, and heterocyclyl, for example. If one factors in combinatorial techniques in making these changes, one skilled in the art will recognize that potentially millions or perhaps tens of millions of "minor" modifications might be prepared.

Thus, Applicants respectfully submit that what one skilled in the art might consider a minor modification, is very far from a finite group of predictable solutions to develop further agents for treating headaches. There would be no motivation to choose Compound I from this limitless group. Applicants suggest that to particularly select Compound I from the teachings of King et al. is completely arbitrary and can only be the product of hindsight knowledge based on the Applicants' disclosure of the compound.

2. There is no guidance in the cited art governing what types of changes to make.

There is no guidance given in King et al. that would lead one skilled in the art to bridge the gap between compound I and the King et al compound. In order to bridge the gap, the skilled artisan is left only with general knowledge of the art for modifying chemical compounds as described above. As established in *Takeda* "it remains necessary to identify **some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness** of a new claimed compound." (*Takeda supra*) Because the Examiner has merely cited an abstract, there is very limited disclosure and certainly nothing providing any impetus to modify the King et al. compound in any particular manner.

3. The differences between Compound I and that of King et al. are large.

In Applicants' first response, Applicants offered substantive differences in structural/electronic/chemical properties that were immediately evident upon inspection of the isomeric compounds alleged by the Examiner to represent minor changes.

First, considering the structural differences, one will note that a substantial portion of the carbon skeleton is shifted in the two isomeric forms, radically changing the molecular topography between the two compounds. The impact of this large structural change alone does not instill one skilled in the art with a reasonable expectation of success in developing a further agent to treat headache. In the best case scenario, one skilled in the art *might* be armed with a crystal structure of a lead compound in an active site of its target. Even with sophisticated modeling, the impact of such a large structural change might not be reasonably predictable. In the present case, a large portion of the molecule is being moved without any knowledge of the pharmacophore or its target.

Secondly, there are significant changes in electrical and chemical properties that would be immediately apparent to one skilled in the art, the impact of which does not imbue one skilled in the art with a reasonable expectation of success. As set forth in the response to the First Office Action, the benzylated nitrogen in King et al. is nominally a benzylic alkyl amine. The benzylated nitrogen claimed is benzylic and allylic. One skilled in the art will recognize that this alteration will change the basicity of the nitrogen atom, the effects of which on the activity of the compound can not be reasonably predicted. From a chemical perspective, the benzylated nitrogen in compound I is placed in proximity to the ring nitrogen allowing for favorable disposition for internal hydrogen bonding or possible chelation of a metal, for example. The effects of these changes in the chemical functionality on the activity can not be reasonably predictable.

4. That there is a reasonable expectation of success is counter to the case law.

As established in *Eisai*, the chemical arts are not likely to be genuinely predictable:

> **To the extent an art is unpredictable, as the chemical arts often are**, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because **potential solutions are less likely to be genuinely predictable**.

Moreover, the present application deals with chemical arts in the unpredictable context of pharmacology. The confluence of structural, electronic and chemical alterations in a pharmacological setting where these molecules interact with biomolecule targets can not be genuinely predictable.

In summary, Applicants take the position that the Examiner has failed to present a *prima facie* case of obviousness under the standards of current chemical case law. The Examiner is deficient in showing a *prima facie* case of obviousness because 1) there was inadequate reasoning presented by the Examiner as to why one skilled in the art would be motivated to use the compound as taught by King et al. as a lead compound for the discovery of the species identified within the claimed genus; 2) the Examiner failed to provide a reason why the skilled chemist would have been motivated to alter the King et al. compound in a particular manner to arrive at the member of the claimed genus; and 3) the Examiner has failed to show that there were a finite number of predictable solutions.

Applicants assert that claims 60, 65, 84, 87, and 90 are all patentable over King et al. for at least these reasons and respectfully request withdrawal of this rejection.

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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